REMARKS

Claims 1-34 are pending.

Claims 15-34, withdrawn in view of Applicants' restriction election, have been cancelled with this Response without prejudice.

New claims 35-40, depending directly or indirectly from claim 1 and fully supported by the original specification, have been added.

Claims 1 and 2 have been amended herein.

Claims 1-14 stand rejected, as allegedly being anticipated by Vasa et al. (Circulation Research 89(1) E1-E7, 06 July 2001) (hereinafter "Vasa"). Applicants herein provide responsive claim amendments and rebuttal arguments to overcome this rejection and, preemptively, any subsequent potential assertion of obviousness that the Examiner my consider.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected claims 1-14, under 35 U.S.C. 102(b), as allegedly being anticipated by Vasa

Vasa. The Examiner states that "Vasa et al., teach an in vitro method for analyzing a sample from a mammal in connection with at least one cardiovascular disease, comparing determining the cardiovascular functionality of the isolated bone- marrow derived precursor cells by means of a migration assay (see entire document, Abstract in particular). Vasa et al., teach that said isolated precursor cells are characterized of expressing Cd34+ , CD133+ and CD45+ (see Materials and Methods in particular). Vasa et al., teach that migration assay was performed in a Boyden-chember using VEGF (see page 2 in particular). Vasa et al., teach that migration

capacity of precursor cell is an independent determinant to predict a cardiovascular functionality of said isolated precursor cells (see overlapping pages 5 and 6 in particular)."

The Examiner, based on the above, concludes that Vasa anticipates Applicants' claimed invention.

Applicants' traversal

Applicants respectfully traverse the rejection.

As an initial matter, Applicants have herein amended independent claim 1 to recite:

> "A method for stratifying mammalian subjects having at least one cardiovascular disease, comprising:
> a) isolating, from a biological sample obtained from a mammalian subject having at least one cardiovascular disease, bone marrow-precursor-cells (BMP) and/or blood-derived circulating precursor-cells (BDP) by means of at least one cell specific surface marker;
> b) performing a cell migration assay on the BMP and/or BDP to provide an assessment of migratory capacity thereof;
> c) determining, based on the assessed migratory capacity, the cardiovascular functionality of the subject's BMP and/or BDP; and
> d) determining, based on the determined cardiovascular functionality, whether the subject would benefit from cell therapy and/or an ex vivo pretreatment of their BMPs or BDPs before retransplantation of the cells to provide for improvement of subject's cardiovascular functionality, wherein a method for stratifying mammalian subjects having at least one cardiovascular disease is afforded."

Basis for this amendment is found in the specification, for example, at paragraph [0004], original claim 16, and generally throughout the entire specification, which is replete with teachings about stratification of subjects as presently claimed.

The publication Vasa is a study showing that the number and migratory activity (VEGF migration assay) of circulating endothelial precursor cells (EPCs) correlate with risk factors for

coronary diseases, such as high blood pressure and smoking. However, Vasa, at page 6, explicitly teaches that "the mechanisms by which risk factors for CAD reduce EPC numbers remain to be determined" and could potentially involve, *inter alia*, "increase apoptosis," "increased oxidative stress," interference with "signaling pathways." Likewise, the mechanism/reason for "decreased migration" is unknown and could possible involve, *inter alia*, "downregulation of VEGF receptor KDR," defects in "downstream signaling," "hypertension," "downregulation of tissue hepatocyte growth factor," "age," LDL cholesterol levels," and "oxidized LDL." Vasa states that while the mechanisms are unknown, the data suggests that "different mechanisms contribute to the impairment in EPC migration compared with the reduced levels of circulating EPCs." Vasa concludes that "taken together, the present study demonstrates that EPC numbers and migratory capacity are impaired in patients with CAD."

Significantly, however, because the prior art including Vasa did not teach or establish a mechanism for the observed reduced EPC numbers and migration, it would be **impossible**, based on the teachings of Vasa to conclude anything about which CAD patients would benefit from cell therapy for example. Likewise, without such a mechanistic nexus, there would have been no reasonable motivation for one skilled in the art to use cell migration capacity of BMP and/or BDP to stratify CAD patients with respect to potential benefit by cell therapy. That is, it could not be anticipated or obvious that a cardiovascular functionality determined by results of cell migration assay, could predict a good cell therapy candidate or a candidate that could benefit from ex vivo treatment of their EPC. As taught in Applicants' specification (e.g., paragraphs [0022] through [0024])—"these were unproven assumptions that were only confirmed in experiments performed in the context of the present invention."

In summary, in contrast to Applicants' presently claimed subject matter, Vasa does not teach, describe or otherwise motivate, *alone or in combination with an other art*, that the determination of the migratory activity of the precursor cells in vitro allows for determining, based on the assessed migratory capacity, the cardiovascular functionality of BMP and/or BDP to provide for a stratification of the patients with regard to a subsequent transplantation of the isolated BMPs and/or BDPs in a therapy of a cardiovascular disease.

A person of ordinary skill in the relevant art would have had no motivation to apply the teaching of Vasa to arrive at Applicants' presently claimed methods. The present invention does not analyze the correlation of risk factors with the number and migratory activity of the precursor cells, but rather determines, based on an assessed migratory capacity, a cardiovascular functionality of BMP and/or BDP, and conceives and validates, for the first time, that this result has substantial utility for stratification (diagnostic/prognostic value) of patients with regard to likely therapeutic benefit of a transplantation of isolated BMPs and/or BDPs in a therapy of a cardiovascular disease. In fact, a person of skill in the art would have been **deterred** by Vasa et al from use of migration value for any such diagnostic/prognostic value because Vasa explicitly teaches that there is an absence of a mechanistic nexus.

Applicants, therefore, respectfully request withdrawal of the rejection in view of the above arguments and claim amendments, because the presently claimed subject matter is neither anticipated nor obviated by the limited "risk factor" teachings of Vasa.

New Claims

New claims 35-40, depending directly or indirectly from claim 1 and fully supported by the original specification including the original claim set thereof, have been added. No new matter has been added.

Applicants contend that the presently amended and new claims are allowable as presented herein. The claims are allowable over the prior art, which does not reasonably teach, convey or otherwise motivate that assessed BMP and/or BDP migratory capacity can be used as a reliable measure for cardiovascular functionality of BMP and/or BDP of a subject to provide for a stratification of the subjects with regard to a subsequent cell therapy such as transplantation of isolated BMPs and/or BDPs in a therapy of a cardiovascular disease.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request entry of the present Response and Amendment, and allowance of all claims as presented herein. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

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Respectfully submitted,
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